Genome Biology

Comment

An issue to remember

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Even by that journal's lofty (and frequently self-proclaimed) standards, the 3 September 2009 issue of *Nature* is likely to be regarded as one of the most memorable in years. Many issues of a general journal have at least one thing in them that is of interest to each reader, but in this case it could be argued that almost everything in this issue is likely to be of interest to practically everybody. Anyone wishing to present evidence of the health of the global scientific enterprise could probably just hold up a copy and then sit down.

Nanotechnology is a field that has sometimes been characterized by more hype than results, but the paper from Nadrian Seeman's lab on page 74 is worthy of all the attention it is likely to attract. It reports the design and synthesis of a triangle of three DNA helices that self-assembles into a three-dimensional periodic array. The authors then prove that the array has the intended structure by crystallizing it and determining its atomic arrangement at 4 Å resolution. As far as I know, this is the first time a well-ordered macromolecular three-dimensional crystalline lattice has been designed and successfully assembled. It opens up the possibility of manufacturing a wealth of nanoscale objects from the stuff that make up the genome, including templates on which other nanoparticles can be assembled. A disclaimer is in order here: Ned Seeman, who is one of the pioneers of biomaterials nanotechnology, has been one of my closest friends for 35 years. I remember when he first described his plans to do this project, over 25 years ago, so this paper is the culmination of more than two decades of effort. But he needs no special favors from me to publicize this work; it is a landmark achievement and if you read nothing else in the article, you should read the last paragraph, in which Ned outlines the possible applications of this technology. It presents a mind-blowing view of a future in which nanoscale fabrication can be done with a precision and versatility that seemed like science fiction not that long ago.

Then there are three papers that represent structural biology at its best, using structure to unveil the details of important cellular mechanisms at the atomic level. They provide the solution of the three-dimensional structure of a mechanosensitive ion channel in its intermediate state, and new insights into the mechanism of action of the molecular motor kinesin, and into the export of tRNA, respectively. In an era when the mindless grinding out of hundreds of structures of proteins of no known function in structural genomics is considered exciting big science and is lavished with support, work such as this reminds us that what structural biologists should be doing is picking important problems and using the power of their technology to probe how things work.

The papers noted so far are enough to make any issue of any journal worth reading, but I haven't even scratched the surface of this one. I will skip over fascinating papers on the molecular basis of the evolution of the heart chamber, and the discovery, in the Andromeda galaxy, of stars and coherent structures that are likely to be the remnants of dwarf galaxies destroyed by the tidal field of this giant one. Two papers stand out as being truly historic. They represent the first reports of the generation of fertile adult mice from induced pluripotent stem cells (iPS cells).

iPS cells are to stem-cell biology what the polymerase chain reaction (PCR) was to cloning. Before PCR, cloning a gene was a hit-or-miss proposition requiring years of work. After PCR, anybody could clone almost anything. Until recently, stem-cell biology was hostage to the technical difficulty, and ethical quagmire, of producing human embryonic stem cells (human ES cells) from human blastocysts. Shinya Yamanaka and his graduate student Katzutoshi Takahashi, from Kyoto University in Japan, changed all that in 2006 when they reported the creation of what they called 'induced pluripotent stem cells'. iPS cells could be generated from a wide variety of differentiated mammalian cells (typically skin cells) by transfection with just four genetic factors. Numerous studies by Yamanaka (who as far as I'm concerned should start booking his flight to Stockholm now to ensure a good seat) and by other workers have confirmed that iPS cells resemble ES cells in morphology, gene-expression profiles, proteomic profile and the epigenetic status of several pluripotency markers. They can also differentiate into a wide variety of specialized cells. But it had not been shown that they could generate viable adult animals.

Until now. On pages 86 and 91 of the 3 September issue of *Nature*, Qi Zhou's and Fanyi Zeng's groups in Beijing and

Shanghai, and Kristin Baldwin and Kristopher Nazor's groups at the Scripps Institute in La Jolla, California, respectively, report the successful generation of healthy, fertile adult mice from iPS cells through tetraploid complementation. A similar result was achieved simultaneously by Shaorong Gao's group at the National Institute of Biological Sciences in Beijing, and was published in the 7 August, 2009 issue of *Cell Stem Cell*. These data prove conclusively that iPS cells are truly pluripotent and that reprogramming differentiated cells with just the four 'Yamanaka factors' can recapitulate the reprogramming capacity of the oocyte.

So it's been done three times, and if it can be done three times it can be done a thousand times, and it certainly will be. iPS cells are going to change the shape of the biomedical world. In my view, all our existing cell-culture models of disease, many of which are generated with inappropriate cell types such as tumor cell lines, need to be re-evaluated in the light of what iPS cells can do. Given the ability to make pluripotent stem cells from easily obtainable cells of a patient with just about any disease, and the relative ease with which those iPS cells can be converted into neurons or liver cells or just about any cell that is needed, the likelihood is that we are on the cusp of a revolution in how we study a host of processes in living organisms.

But I have to say that none of the papers I've talked about so far is my favorite (sorry, Ned). On page 53 of this remarkable issue is the one I enjoyed the most: 'Early-warning signals for critical transitions' by Marten Scheffer at Wageningen University in the Netherlands and a host of colleagues from other countries. This paper lays out a set of critical signs that a complex system - whether the climate, the brain circuitry of an epileptic, or the financial markets - is about to undergo a dramatic shift from one state to another. If the financial 'masters of the Universe' had only been able to read this paper before the recent financial crisis - well, OK, being a bunch of greedy morons they probably wouldn't have understood it and almost certainly wouldn't have paid attention to it even if they had. Still, for anyone who wants to see when something big is about to happen, the paper is riveting. The authors develop a mathematical model of transitions that provides support for their conclusions, but their essential concepts are easily understood in non-mathematical terms. Basically, systems about to undergo significant transitions experience critical slowing down, increased asymmetry of fluctuations ('skewness'), oscillation between two substates ('flickering'), and the appearance of particular spatial patterns. The authors go on to show that these early-warning signals can predict the onset of transitions in people prone to asthmatic and epileptic seizures, the end of glacial periods, changes in direction of the financial markets, and a number of other real-world applications.

Obviously, I really enjoyed reading this issue of *Nature*, and the point I now want to make is that I wouldn't have read it at all if I hadn't happened to read it. Let me explain. I knew that Ned had an important paper coming out soon, so I scanned the table of contents of each issue of *Nature* for a couple of weeks. That in turn caused me to notice the papers by Zhou and Steffen and all the others. But had I instead searched for Ned's paper online, I would have missed them. True, I might have found the iPS cell papers eventually because I am interested in that topic, but I never would have read the early-warning signal paper, or the tRNA export factor paper, or most of the other papers I've talked about here.

Picking up a copy of a journal and thumbing through it - browsing, as we used to call it - has gone out of fashion with the advent of electronic databases and searching the literature with Google or PubMed. That may be more efficient but it's a lot less fun. Creativity is the art of the unexpected, of putting disparate facts together, of connecting the dots between two fields where connections are not known to exist. The more precise our searching, the more specialized our knowledge, the less chance there is of the happy accident from which new ideas almost always spring.

In the rush to do away with paper copies of journals and move towards all-online publication (like this journal), we are in danger of forgetting the importance of finding ways to keep browsing alive. As long as paper copies of journals exist, I will try to find the time to flip through them, hoping for that happy accident. Precise searching within the confines of one's field certainly helps to create experts, but I am willing to bet that those who arrange their intellectual lives so that they only find what they are looking for will forever work for those who browse.

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